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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/709,170
Filing Date: November 10, 2000
Appellant(s): WARRELL ET AL.

WARRELL et al.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 22, 2008 appealing from the Office action mailed March 25, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

In response to an amendment, a Final Office Action was mailed stating that claims 1, 3-5, and 7-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., in view of Waters et al. and Bennett et al.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the Examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, and 7-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141), in view of Waters et al. (Journal of Clinical Oncology, 2000 Vol. 18:1812-1823) and Bennett et al. [U.S. Patent No: 6,214,986].

Claims 1, 3-5, and 7-17 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in more than one cycle of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by

an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day, and further comprises administering one or more cancer therapeutics. Claim 18 is drawn to a specific bcl-2 antisense oligonucleotide comprising SEQ ID NO:17. Claims 19-23 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in more than one cycle of therapy, each cycle of therapy consisting of 3 to 9 days, in combination with a chemoagent, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day. It is noted that Applicant's specification, at page 6, forth paragraph discloses: "[A]s used herein, the phrases "treating cancer" and "treatment of cancer" mean to… decrease tumor size".

Webb et al. teach bcl-2 antisense therapy at a dose from 4.6 mg/m^2 to 73.6 mg/m^2 in human patients with non-Hodgkin lymphoma (see Abstract). Specifically, Webb et al. disclose the reduction of bcl-2 protein levels in the lymph node aspirates of Patient 6 after a 7 day course of therapy and a 14 day course of therapy using a fully phosphorothioated bcl-2 antisense (see Figure 2). It is noted that the fully phosphorothioated bcl-2 antisense oligonucleotide disclosed by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. also teach that after a 14 day course of therapy, both Patient 6 and Patient 8 exhibited an improvement in symptoms and tumor shrinkage (see Table 3).

Webb et al. do not teach more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered, wherein said interval

of time comprises at least one day, and wherein said therapy further comprises administering one or more cancer therapeutics or chemoagents and at specific doses.

Waters et al. teach bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma for the purpose of monitoring drug toxicity, treatment efficacy, and response. For example, Waters et al. teach that one course of treatment was planned per patient, but additional courses of treatment were considered in the event of a tumor response (see page 1813, first column, mid-column). Waters et al. also teach that "[O]ther trails of antisense oligonucleotides in malignant disease have investigated repeated courses of therapy over protracted periods of time" (see page 1819, second column). Waters et al. also suggest using bcl-2 antisense oligonucleotides in combination therapy with other chemotherapeutic agents (see page 1820, second column, last paragraph and also see page 1822).

Bennett et al. teach the antisense modulation of bcl-x expression using therapeutic compositions comprising antisense oligonucleotides. It is noted that bcl-x is a closely-related family member of bcl-2, as bcl-x was isolated using a bcl-2 cDNA probe at low stringency due it its sequence homology with bcl-2 (see column 1, lines 39-43). Bennett et al. also teach antisense oligonucleotides are administered with one or more cancer therapeutics that function by a non-antisense mechanism, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. teach:

> "[T]he formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several

> months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the Patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16 and17, last and first paragraphs, respectively).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to devise a method of treating cancer in a human comprising administering a bcl-2 antisense using the teachings of Webb et al. It would have been *prima facie* obvious to administer the antisense in a cycle of therapy comprising 3 to 9 days using the teachings of Bennett et al. It would have been *prima facie* obvious to one of ordinary skill in the art to administer the antisense in more than one cycle of therapy in view of the teachings of Waters et al. It would have been *prima facie* obvious to have the more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered in view of either Waters et al. or Bennett et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the antisense therapy further comprising administering one or more cancer therapeutics or chemoagents using the teachings of Waters et al. and Bennett et al.

One of ordinary skill in the art would have been motivated to devise a method of treating cancer in a human comprising administering a bcl-2 antisense since Webb et al.

taught the success of such a method in treating patients with non-Hodkin's lymphoma. One of ordinary skill in the art would have been motivated to administer the antisense in a cycle of therapy comprising 3 to 9 days since Bennett et al. taught that dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Further, Bennett et al. taught that persons of ordinary skill can easily determine [emphasis added] optimum dosages, dosing methodologies and repetition rates.

One of ordinary skill in the art would have been motivated to have the more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered since Waters et al. taught bcl-2 antisense oligonucleotide therapy for the purpose of monitoring drug toxicity, treatment efficacy, and response. Further, one of ordinary skill in the art would have been motivated to have the more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered since the prior art taught that persons of ordinary skill can easily determine repetition rates (see Bennett et al.).

One skilled in the art would have been motivated to administer the antisense therapy with one or more cancer therapeutics or chemoagents as taught by Bennett et al. and Waters et al. and since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment. One of ordinary skill in the art would have been motivated to vary the cycles of therapy or to vary the antisense dosage amount since it is routine and well known in the art to determine optimum

dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues as taught by either Webb et al., Waters et al., or Bennett et al.

One of ordinary skill in the art would have expected success at devising a method of treating cancer in a human comprising administering a bcl-2 antisense since Webb et al. taught the successful use and design of such a method. One of ordinary skill in the art would have expected success at administering the antisense in a cycle of therapy comprising 3 to 9 days since Bennett et al. taught that persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Further, one of ordinary skill in the art would have expected success at administering the antisense in a cycle of therapy comprising 3 to 9 days using nothing more than routine experimentation and testing.

One of ordinary skill in the art would have expected success at having the more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered since Waters et al. taught how to successfully monitor bcl-2 antisense toxicity, pharmacokinetics, and efficacy. Further, one of ordinary skill in the art would have expected success at having the more than one cycle of therapy separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered since Bennett et al. taught that the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. One of ordinary skill in the art would have expected success at administering the antisense therapy with one or more cancer therapeutics or since Bennett et al. taught

how to successfully use antisense compounds with one or more other chemotherapeutic agents which function by a non-antisense mechanism as a means to treat cancer.

Therefore the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's filing.

(10) Response to Argument

Appellants firstly argued that Webb in view of Waters and Bennett does not suggest to one skilled in the art a method of treating cancer in a human because the elements of "more than one cycle of therapy", "3 to 9 days", and "separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered" are missing from the cited art. For example, Appellants argue that Webb discloses administration of bcl-2 ASO for 14 days, whereas the claims recite administration of bcl-2 ASO for 3-9 days. Furthermore, Appellants argue that Tab A, which is Dr. Novick's declaration provides examples of the prior art showing that the generally accepted course of bcl-2 ASO therapy was a 14-day treatment regimen. Appellants argue that based on the teachings of Webb et al. and the Novick declaration, one skilled in the art would not be motivated to shorten the course of therapy from the 14 day course of therapy taught by Webb and exemplified in the prior art.

Response:

In response to Appellant's first argument, it should be noted that the Examiner did not rely on Webb to suggest shortening a cycle of therapy to 3 to 9 days. Instead, this motivation came from the explicit teachings of Bennett et al. who taught that,

regarding antisense oligonucleotide therapy, persons of ordinary skill in the art can easily [emphasis added] determine repetition rates. Additionally, Bennett et al. teach that dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Therefore, given the teachings of Bennett, it is the Examiner's position that one skilled in the art would be motivated to shorten the 14 day cycle of therapy taught by Webb et al. and exemplified in the prior art, depending on the severity of the disease and depending on the responsiveness of the disease.

Furthermore, is the Examiner's position that one skilled in the art, using nothing more than the teachings of the prior art, which explicitly mentions courses of at least a few days (per Bennett), to conduct routine experimentation and testing that would result in a shorter course of therapy than the 14-day course of Webb. For these reasons, it is believed that Bennett satisfies Appellants arguments regarding "3 to 9 days" and "separated by an interval of time where no bcl-2 antisense oligonucleotide is administered".

Appellants secondly argued that the it is improper for the Examiner to conclude that subject matter cannot be patented on the basis of an inherent property. Appellants argue that the principle of inherency relied upon in the instant § 103 rejection has no place.

Response:

In reponse to Appellant's second argument, the Examiner disagrees that inherency has no place in the instant § 103 rejection. This is primarily because the claims are directed to administering bcl-2 antisense for 3-9 days, where Webb et al. disclose administration for a total of 14 days, but also disclose results of bcl-2 protein expression after only 7 days in Patient 6 (see Figure 2). Because of this disclosure, the Examiner was relying on the inherency argument because, in her eyes, the results of bcl-2 protein expression after only 7 days in Patient 6 amounted to administering bcl-2 antisense for 3-9 days as recited in Appellant's claims.

However, without acquiescing to Appellant's arguments, and solely in the interest of concentrating on the main focus of the instant § 103 rejection, as the Examiner was not relying on the inherency doctrine to base the rejection, the argument of inherency made by Appellant's is rendered moot. For clarity, the argument of inherency made by Appellant's is moot in view of the fact that the Examiner is not relying on inherency as the basis for the § 103 rejection of record. Instead, as discussed below, the basis and the main focus of the rejection surrounds the fact that Webb et al. taught a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide in a cycle of therapy comprising 14-days. Waters et al. provided motivation to administer the antisense oligonucleotide in more than one cycle of therapy. Bennett et al. provide motivation to shorten the 14-day course of therapy taught in the prior art. Furthermore, it is the Examiner's position that one skilled in the art, using nothing more than routine experimentation and testing, would be motivated to shorten the 14-day

course of therapy taught in the art. Waters et al. and Bennett et al. independently provide the motivation to have the more than one cycle of therapy separated by an interval of time wherein the no bcl-2 antisense oligonucleotide is administered. For the reasons above, it is the Examiner's position that the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of Appellant's filing.

Appellants thirdly argued that the claims are directed to what is known as "intermittent" therapy where, for example, the discontinuance of therapy in patient 17 of Waters due to toxicity, with the intentional and desired intermittent therapy recited in the instant claims, distorts the meaning of the term beyond all comprehension. Appellants argue that the Novick declaration notes that there is nothing to teach or suggest that patient 17's second course of therapy at low dose was anything but the planned 14-day cycle required by the Waters protocol. Also, Appellants argue that there is no indication that any interval of time in which no bcl-required was administered separated the treatment courses of therapy, as required by the instant claims. As such, Appellants argue that it can hardly be said that Waters provides the motivation to one skilled in the art to administer bcl-2 ASO in an intermittent fashion to achieve clinical benefits.

Response:

In reponse to Appellant's third argument, it is quite clear that Waters et al. teach antisense oligonucleotide therapy for the purpose of monitoring drug toxicity, treatment efficacy, and response. In fact, Waters et al. explicitly teach:

> "[O]ne course of treatment was planned per patient, but additional courses of treatment were considered in the event of a tumor response (see page 1813, first column, mid-column).

Now then, considering the latter, it is the Exmainer's position that one skilled in the art would be motivated to administer the antisense oligonucleotide in more than one cycle of therpay. Furthermore, based on the teachings of Waters, one skilled in the art would be motivated to have an interval of time in which no bcl-2 ASO is administered to evaluate the pharmacokinetics and toxicity of the antisense therapeutic and to determine efficacy. For these reasons, it is believed that Waters satisfy Appellants arguments regarding "more than one cycle of therapy" and "separated by an interval of time where no bcl-2 antisense oligonucleotide is administered".

Appellants fourthly argued that Bennett discloses the use of bcl-x ASOs, whereas the claims are directed to bcl-2 ASOs. Appellants argue that the Examiner has provided no extrinsic evidence that determining the optimum dosages, dosing methodologies, and repetition rates for bcl-x has any applicability to the administration of bcl-2.

Response:

In reponse to Appellant's fourth argument, Bennet make clear that bcl-x is a closely-related family member of bcl-2, as bcl-x was isolated using a bcl-2 cDNA probe at low stringency due it its sequence homology with bcl-2 (see Bennett column 1, lines 39-43). While it is recognized that bcl-2 and bcl-x are entirely different proteins, it should be noted that the two proteins are commonly regulators of apoptosis and overexpressed in various cancers (see Bennett column 1, line 17 through column 3, line

59). However, assuming *arguendo* that bcl-2 and bcl-x were not related proteins, the Examiner relied on Bennett to primarily teach that the formulation of antisense therapeutic compositions and their subsequence administration is believed to be within the skill of those in the art.

Appellants fifthly argued that the boilerplate disclosure of ASO dosing as in Bennett does not suggest to one skilled in the art the claimed 3-9 day treatment period, even in view of Webb. Appellants allege that the Examiner's reliance on the superficial teachings of Bennett regarding optimizing dosing schedules amounts to a mere allegation of obviousness. Appellants rely on the Novick declaration which is of the opinion that one skilled in the art would not have shortened the 14 day cycle in Webb, regardless of Bennett's boilerplate language regarding optimal dosing of ASOs. Appellants contend that it was not until after Appellants' invention that others moved to shorter cycles of therapy.

Response:

In reponse to Appellant's fifth argument, it should be noted that Webb et al. explictly teach:

> "[O]ur findings are encouraging and warrant further investigations of bcl-2 antiense therapy in cancer treatment" (see page 1137 @ Interpretation).

The evidence of record shows that it is routine in the art to optimize dosing schedules and that persons of ordinary skill can easily determine [emphasis added] repetition rates (see Bennett). Webb et al. teach a 14 day course of antisense therapy improved

symptoms and treated cancer. Given these disclosures, it is the Examiner's position that the optimization of the 14 day course of therapy of Webb et al. would flow from the "normal desire of scientists or artisans to improve upon what is already generally known." See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Therefore, one skilled in the art would be motivated to shorten the 14 day course of therapy of Webb et al. in view of the teachings of Bennett combined with mere routine experimentation.

Appellants sixthly argued that even if the references were combined in the fashion submitted by the Examiner, it still would not suggest to one skilled in the art the claimed invention with all its limitations. Appellants rely on the Novick declaration which makes clear that one skilled in the art would not have shortened the 14-day cycle in Webb. Appellants contend that rather, the skilled artisan would have continued with longer courses of therapy given the overall unsatisfactory results provided in Webb and Waters. Appellants contend that the Examiner has used hindsight reasoning to base the instant rejection.

Response:

In reponse to Appellant's sixth argument, the Examiner disagrees that the results of Webb were "overall unsatisfactory" as opinioned in the Novick declaration. This is primarily due to the fact that Appellant's specification, at page 6, discloses:

> "[A]s used herein, the phrases "treating cancer" and "treatment of cancer" mean to… decrease tumor size".

Now then, referring to Webb, Table 3 clearly shows that Patient 6 and Patient 8

exhibited an improvement in symptoms and tumor shrinkage. Thus, in view of Appellant's specific definition of the term "treating cancer", it is unclear how the results of Webb were deemed "unsatisfactory".

Regarding hindsight reasoning, it should be noted that it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the prior art taught that a bcl-2 antisense oligonucleotide could be used to treat cancer (see Webb). The evidence of record also taught the desire to administer the antisense oligonucleotides in more than one cycle of therapy (see Waters). Bennett taught that regarding antisense oligonucleotide therapy, it is routine in the art to optimize dosing schedules and that persons of ordinary skill can easily determine [emphasis added] repetition rates and optimum dosing. In addition to Bennett, it is the Examiner's position that one skilled in the art, using nothing more than routine experimentation and testing, would be motivated to shorten the 14-day course of therapy taught in the art. Therefore, it is the combination of Webb, Waters and Bennett, and not hindsight reasoning that the Examiner has based the § 103 rejection of record.

Appellants lastly argued that the Examiner's rejection appears to rest on nothing more than the assertion that it is always obvious to modify a therapeutic dosing

regiment to achieve optimal results, even in the face of teachings to the contrary. Appellants assert that the Examiner appears to have overemphasized the so-called "routine" nature to establish and support the claimed method of treatment, particularly after its acceptance by others in the art. In this regard, Appellants argue that the Examiner has failed to give proper weight to the nonobviousness of the invention "as a whole" under § 103 and has failed to make out a *prima facie* case of obviousness.

Response:

In reponse to Appellant's last argument, it should be noted that the Examiner gave proper weight in determining whether the claimed invention as a whole would have been obvious. As discussed *supra*, Webb et al. taught a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide in a cycle of therapy comprising 14 days. Waters et al. provided motivation to administer the antisense oligonucleotide in more than one cycle of therapy. Bennett et al. provide motivation to shorten the 14-day course of therapy taught in the prior art. Furthermore, it is the Examiner's position that one skilled in the art, using nothing more than routine experimentation and testing, would be motivated to shorten the 14-day course of therapy taught in the art. Waters et al. and Bennett et al. independently provide the motivation to have the more than one cycle of therapy separated by an interval of time wherein the no bcl-2 antisense oligonucleotide is administered. For the reasons above, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been *prima facie* obvious at the

time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Therefore, it is believed that the rejections should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's Answer.

Respectfully submitted,

/Terra Cotta Gibbs/
Art Unit 1635

Conferees:

/JD Schultz/
Supervisory Patent Examiner, Art Unit 1635

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632